Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome

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ABSTRACT

Objective: To evaluate efficacy and safety of clobazam, a 1,5-benzodiazepine, as adjunctive therapy for Lennox-Gastaut syndrome (LGS).

Methods: Patients aged 2–60 years were randomized to placebo or clobazam 0.25, 0.5, or 1.0 mg/kg/day. Study consisted of 4-week baseline, 3-week titration, and 12-week maintenance phases, followed by a 2- or 3-week taper or continuation in an open-label extension. Primary endpoint was percentage decrease in mean weekly drop seizure rates during maintenance vs baseline phases for modified intention-to-treat (mITT) population. Secondary outcomes included other seizure types, responder rates, and physicians’ and caregivers’ global assessments.

Results: A total of 305 patients were screened, 238 were randomized, and 217 composed the mITT population. Of patients enrolled after a protocol amendment, 125/157 (79.6%) completed. Average weekly drop seizure rates decreased 12.1% for placebo vs 41.2% (p = 0.0120), 49.4% (p = 0.0015), and 68.3% (p < 0.0001) for the clobazam 0.25-, 0.5-, and 1.0-mg/kg/day groups. Responder rates (≥50%) were 31.6% (placebo) vs 43.4% (p = 0.3383), 58.6% (p = 0.0159), and 77.6% (p < 0.0001) for clobazam 0.25-, 0.5-, and 1.0-mg/kg/day groups. Physicians’ and caregivers’ assessments indicated clobazam significantly improved symptoms. Somnolence, pyrexia, upper respiratory infections, and lethargy were the most frequent adverse events reported for clobazam.

Conclusions: Clobazam significantly decreased weekly drop seizure rates in LGS. No new safety signals were identified.

Classification of evidence: This study provides Class II evidence that clobazam as adjunctive therapy is efficacious, in a dosage-dependent manner, in reducing mean weekly drop seizure rates of patients with LGS over 12 weeks. Neurology® 2011;77:1473–1481

GLOSSARY

AE = adverse event; CI = confidence interval; GERD = gastroesophageal reflux disease; LGS = Lennox-Gastaut syndrome; mITT = modified intention-to-treat; OLE = open-label extension; OR = odds ratio; SAE = serious adverse event.

Lennox-Gastaut syndrome (LGS) is a severe childhood epileptic encephalopathy characterized by a classic triad of 1) frequently generalized, slow spike-and-wave EEG, 2) several seizure types, and 3) developmental delay and behavioral disturbances.1 Onset generally occurs before 8 years of age, with peak occurrence between 3 and 5 years. LGS seizures are predominantly tonic, atonic, and atypical absence, and patients are often refractory to antiepileptic drugs.2 Clobazam, a 1,5-benzodiazepine, is available as adjunctive therapy for epilepsy and anxiety disorders in >100 countries.3 It has been in US clinical development for LGS since 2005.3 In a phase II study, clobazam was well-tolerated and decreased weekly rates of drop and nondrop seizures for patients with LGS.4 Clobazam 1.0 mg/kg/day was more efficacious than clobazam
0.25 mg/kg/day. In the high-dosage group, mean (median) decrease in weekly drop seizure rate was 85% (93%), and 83% of those patients had ≥50% decreases in weekly rates of drop seizures. Clobazam’s efficacy as adjunctive LGS therapy has been notable.5–9 Similarly, a ≥50% responder rate of 56.3% was obtained in a pooled analysis of 80 patients with LGS from 8 open-label studies.3

This Phase III, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of CLObazam in PatieNTs with Lennox-GAStaut SyNdrome (CONTAIN) further assessed the efficacy and safety of clobazam as adjunctive therapy. The primary objectives were to determine 1) efficacy of 3 dosages in decreasing weekly frequencies of drop and total seizures during a 12-week maintenance phase vs baseline and 2) safety of clobazam when administered ≤18 weeks at 3 dosages.

METHODS Patients. Patients aged 2–60 years weighing ≥12.5 kg were eligible to participate in the CONTAIN trial if they had onset of LGS before 11 years of age. A clinical diagnosis of LGS was evidenced by ≥1 type of generalized seizure (including drop seizures) for ≥6 months and a previous EEG report documenting generalized, slow spike-and-wave (<2.5 Hz) patterns.1 Study inclusion and exclusion criteria are provided in appendix e-1 on the Neurology® Web site at www.neurology.org.

Standard protocol approvals, registrations, and patient consents. The study (ClinicalTrials.gov identifier: NCT00518713) was approved by an independent ethics committee or institutional review board at each study site. Written, informed consent was obtained from each patient or the patient’s parent/caregiver.

Study design. This phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial was conducted at 51 sites in the United States, India, Europe, and Australia between August 2007 and December 2009. The study included 4-week baseline, 3-week titration, and 12-week maintenance periods, followed by either continuation in an open-label study or a 2- or 3-week taper period, depending on weight, with a follow-up visit 1 week after last dose (figure 1).

On day −1, patients were stratified by weight (12.5 kg to ≤30 kg, >30 kg) and randomly assigned (through central randomization via interactive voice response system) to one of 4 groups: 1) placebo; 2) low-dosage clobazam: target of 0.25 mg/kg/day (maximum, 10 mg/day); 3) medium-dosage clobazam: target of 0.5 mg/kg/day (maximum, 20 mg/day); or 4) high-dosage clobazam: target of 1.0 mg/kg/day (maximum, 40 mg/day). Clobazam 5-mg tablets and matching placebo tablets were supplied. During titration, clobazam 5 mg/day or 10 mg/day or placebo (in divided doses) was initiated, and dosage was increased per schedule every 7 days until the assigned target dosage was attained. At any time beginning with week 1 during titration, investigators could decrease daily dosages by a single tablet (placebo or clobazam 5 mg/day) if patients developed any signs or symptoms representing difficulty tolerating study drug.

Protocol amendment. At study inception, the protocol permitted patients to easily discontinue from OV-1012 (CONTAIN) and enter an open-label extension (OLE). This led to many premature discontinuations within 4 weeks of starting therapy. To address this issue, the study protocol was revised in October 2008, after 81 patients had enrolled. With the amendment, patients whose seizures worsened were required to have completed week 9 of the study (i.e., after an adequate trial of study drug) before discontinuing and entering the OLE.
Efficacy assessments. The primary efficacy endpoint was percentage decrease in the average weekly rate of drop seizures from the 4-week baseline period to the 12-week maintenance period. Drop seizures were recorded by patients’ parents/caregivers in daily seizure diaries. Drop seizure was defined as a drop attack or spell involving the entire body, trunk, or head that led to a fall, injury, slumping in a chair, or the patient’s head hitting a surface or that could have led to a fall or injury, depending on the patient’s position at the time of the attack or spell. Drop seizures were recorded as a single seizure (occurring ≥15 minutes before and after the next seizure) or cluster of seizures (≥2 drop seizures with <5 minutes between any 2 consecutive seizures). For clusters, an exact number of drop seizures or a seizure range (10–20 drop seizures or >20 drop seizures) could have been recorded.

Secondary efficacy assessments included percentage decreases in average weekly rate of nondrop seizures (classified according to International League Against Epilepsy guidelines) and total (drop and nondrop) seizures; responder rates (percentages with ≥25%, ≥50%, ≥75%, and 100% decreases in drop seizures from baseline to maintenance period); and physicians’ and caregivers’ global evaluations of the patients’ overall changes in symptoms over time (using a 7-point Likert scale, with 1 = very much improved and 7 = very much worse). Of note, tonic-clonic seizures that did not result in drop attacks were counted as nondrop seizures.

Safety assessments. Safety assessments included laboratory assessments (chemistry, hematology, and urinalysis), physical and neurologic examinations, vital sign monitoring, EKG monitoring, and adverse event (AE) assessment.

Statistical analyses. For information on statistical analyses, see appendix e-2.

RESULTS Patient disposition and baseline results. A total of 238 patients were randomized, including 165 patients at 33 sites in the United States, 55 patients at 13 sites in India, and 18 patients at 5 sites in Europe and Australia; 177 patients (74.4%) completed the study (figure 2). At the time of the amendment, 81 patients had enrolled. Of these, 29 (36%) discontinued, 26 before the amendment went into effect and 3 after. Twenty-three of those 29 entered the OLE. Following the amendment, 157 patients en-
rolled, of which 32 (20%) discontinued. Further, 9 of these 32 entered the OLE. The most common reasons for discontinuing the study were lack of efficacy for placebo-treated patients and AEs for clobazam-treated patients. All 238 randomized patients were included in the safety population. The mITT population excluded 21 patients who did not have daily seizure measurement during the maintenance period. Thus, efficacy analyses included 217 patients (57 for placebo and 53, 58, and 49 for the low-, medium-, and high-dosage clobazam groups).

Demographics and baseline characteristics were comparable between groups (table 1) and were similar between the safety and mITT populations. Mean age was 12.4 years (range, 2–54 years), and the majority (60.5%) were male. Approximately 50% of all patients were receiving concomitant valproic acid, valproate semisodium, or valproate sodium.

### Table 1 Demographics and baseline characteristics (safety population)

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<td>40 (16.8)</td>
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<td>Baseline average weekly drop seizure ratea</td>
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*a* Excludes one patient in the medium-dosage group with no single drop seizure data.

**Primary efficacy.** The mean percentage decrease in average weekly rate of drop seizures from baseline to maintenance period was 12.1% for placebo vs 41.2% ($p = 0.0120$), 49.4% ($p = 0.0015$), and 68.3% ($p < 0.0001$) for the clobazam 0.25-, 0.5-, and 1.0-mg/kg/day groups (figure 3A). Mean differences from the placebo group increased with increasing clobazam dosage (mean differences of 29.1%, 37.3%, and 56.1% for the low-, medium-, and high-dosage groups). There was a linear trend ($p < 0.0001$) of increasing efficacy with increasing dosage.

**Secondary efficacy.** Percentage decreases in weekly rates of total and nondrop seizures. The mean percentage decrease in average weekly rate of total (drop and nondrop) seizures was 9.3% for placebo vs 34.8% ($p = 0.0414$), 45.3% ($p = 0.0044$), and 65.3% ($p < 0.0001$) for the clobazam 0.25-, 0.5-, and 1.0-mg/kg/day groups (figure 3B).

Average weekly rates of nondrop seizures increased 76.3% for placebo, 53.3% for the low-dosage clobazam group, and 3.3% for the medium-dosage clobazam group; and decreased 40.0% for the high-dosage clobazam group (differences not significant by analysis of covariance model). Mean differences in seizure reductions for the placebo group increased with increasing dosage of clobazam (absolute mean differences of 23.0%, 73.0%, and 116.3% for the low-, medium-, and high-dosage groups). The rank-transformed percentage decrease in weekly rates of
nondrop seizures was greater for the high-dosage group vs placebo ($p = 0.0070$).

**Responder rates.** Responder rates increased with increasing clobazam dosages (figure 4). The percentage of patients with ≥50% decreases from baseline to maintenance period in average weekly rate of drop seizures was 31.6% (18 of 57 patients) for placebo vs 43.4% (23 of 53 patients), 58.6% (34 of 58 patients), and 77.6% (38 of 49 patients) for the low-, medium-, and high-dosage clobazam groups, respectively. The likelihood of achieving ≥50% response was greater for the medium-dosage (odds ratio [OR] 2.8; 95% confidence interval [CI] 1.2–6.5; $p = 0.0159$) and high-dosage (OR 7.5; 95% CI 3.0–18.5; $p < 0.0001$) clobazam groups compared with the placebo group.

Two patients (3.5%) in the placebo group were seizure-free (100% decrease from baseline in drop seizure rates), compared with 4 (7.5%), 7 (12.1%), and 12 (24.5%) patients for the low-, medium-, and high-dosage clobazam groups. Because of the relatively small numbers of patients in these groups, logistic regression models were unable to provide valid statistical comparisons for the 100% response threshold.

**Physicians’ and caregivers’ global evaluations.** All 3 clobazam dosages led to improvements in physicians’ and caregivers’ global evaluations of patients’ overall changes in symptoms from baseline to week 15/end of treatment (figure e-1). The percentages of patients who were at least minimally improved ranged from 71.2% to 80.7% (physicians’ assessments) and 79.2% to 81.6% (caregivers’ assessments) for clobazam vs 47.3% (physicians’ assessments) and 45.5% (caregivers’ assessments) for placebo. Similarly, percentages of patients who were much improved or very much improved ranged from 46.2% to 64.9% (physicians’ assessments) and 41.5% to 59.2% (caregivers’ assessments) for clobazam vs 23.6% (physicians’ assessments) and 25.5% (caregivers’ assessments) for placebo.

**Safety.** The percentages of patients with ≥1 AE were 67.8% for placebo, 72.4% for the low-dosage group, 88.7% for the medium-dosage group, and 76.3% for the high-dosage group. AEs experienced by ≥5% of patients in any treatment group are provided in table e-1. AEs with ≥10% difference between placebo and any clobazam group were somnolence, pyrexia, lethargy, drooling, and constipation. Sedation was reported for 8 (4.5%) clobazam-treated patients (1 in the low-dosage group, 2 in the medium-dosage group, and 5 in the high-dosage group). Of these AEs, somnolence and drooling increased in frequency with increasing clobazam dosage.

A dosage-related trend was observed for the overall incidence of AEs leading to discontinuation.
Twenty-seven patients (2 in the placebo group, 4 in the low-dosage group, 8 in the medium-dosage group, and 13 in the high-dosage group) discontinued because of AEs. Treatment-emergent AEs that led to premature discontinuation for \( \geq 2 \) patients were lethargy, somnolence, aggression, ataxia, insomnia, and fatigue.

Few patients reported new seizure types (2 in the placebo group, 1 in the low-dosage group, 2 in the medium-dosage group, and 3 in the high-dosage group). There were 2 serious AEs (SAEs) related to seizures (myoclonic epilepsy for 1 patient in the medium-dosage group and grand mal convulsion for 1 patient in the high-dosage group).

Sixteen patients experienced SAEs (2 in the placebo group and 3, 6, and 5 in the low-, medium-, and high-dosage groups, respectively) (table e-2). SAEs for \( \geq 2 \) patients were lobar pneumonia (1 in the placebo group and 2 in the high-dosage group) and pneumonia (2 in the low-dosage group, 2 in the medium-dosage group, and 1 in the high-dosage group). No deaths were reported.

Few treatment-emergent AEs associated with abnormal clinical laboratory results considered to be at least possibly related to study drug (thrombocytopenia and increased eosinophil count) were reported. No clinically meaningful trends were observed for clinical laboratory assessments, vital signs, EKG or EEG results, or in physical and neurologic examinations.

Twenty-nine patients had their dosages decreased at some point during the study because of an AE. Of these 29, 1 patient was in the placebo group, and 4, 9, and 15 patients were in the low-, medium-, and high-dosage groups, respectively. Ten of 29 discontinued because of an AE (1, 4, and 5 patients in the low-, medium-, and high-dosages groups.)

DISCUSSION In the CONTAIN trial, the largest study conducted in LGS, clobazam was efficacious as adjunctive therapy for drop seizures associated with LGS in patients aged 2 to 54 years. Safety was as anticipated, based on previous clinical studies of clobazam.

Decreases in mean (median) weekly rates of drop seizures from 4-week baseline to the 12-week maintenance phase with clobazam were substantial and significant. There was a linear trend of increasing efficacy with increasing dosage. In contrast with previous studies that compared placebo with a titrated dosage of active drug,\(^5\text{-}\text{9}\) this phase III study was a true dosage-ranging study, enabling evaluation of benefit/risk ratios of lower and higher dosages of clobazam.

All 3 clobazam dosages decreased weekly rates of total (drop and non-drop) seizures. Decreases were driven mainly by drop seizures. Of patients in the high-dosage group, approximately 3 of 4 had at least a 50% decrease and approximately 1 of 4 had a 100% decrease. Moreover, decreases in seizure frequency with clobazam were accompanied by significant improvements in LGS.

Percentages of patients with \( \geq 25\% \), \( \geq 50\% \), \( \geq 75\% \), and 100% decreases from baseline to maintenance period in average weekly rate of drop seizures increased with increasing clobazam dosage. The logistic regression model was unable to provide valid estimates of statistical significance for the 100% response threshold. *\( p < 0.01 \) vs placebo. **\( p < 0.05 \) vs placebo.
symptoms, as assessed by global evaluations by physicians and parents/caregivers.

Currently, 5 AEDs (clonazepam, felbamate, lamotrigine, topiramate, rufinamide) have demonstrated clinical efficacy and are approved by the FDA for LGS.5–9,11–17

No new safety issues were identified. AEs were as expected, given what is known about clobazam from extensive previous clinical development efforts.4,18–23 It has been suggested there are different incidences and severities of sedation between clobazam and other benzodiazepines.23–26 While some have hypothesized this observation is a result of differential binding of receptors,27,28 the clinical validity of these hypotheses could not be tested in this study, given that comparator data were not generated.

Patients were tapered off clobazam by decreasing total daily dosages up to 20 mg/day on a weekly basis. During this tapering, withdrawal symptoms were not observed. In addition, there was no evidence of status epilepticus or severe seizure exacerbation. In clinical practice, physicians may choose to taper patients at the same rate or more slowly than the 2- to 3-week period employed in this study. Pneumonia was the only SAE occurring for more than a single patient during the study.

Nine patients had pneumonia (any type) reported as an SAE. For 4 of these 9 patients, 3 had a history of gastroesophageal reflux disease (GERD), 2 had a history of G-tube placements, and 2 had a history of drooling (patients may have had more than one event). These findings should be interpreted with caution, but suggest there may be an association between presence of GERD, G-tubes, and drooling and occurrence of pneumonias in patients with LGS.

The present 15-week study is insufficient for evaluating clobazam as long-term adjunctive therapy for LGS. An OLE is underway to assess the long-term effects of clobazam in patients with LGS. All patients from CONTAIN who entered the OLE received clobazam 0.5 mg/kg (maximum of 40 mg/day) for 2 days. Then the dosage could be adjusted to a maximum of 2.0 mg/kg/day (maximum of 80 mg/day). A total of 267 patients enrolled in the OLE: 61 of 68 patients from the phase II study and 206 of 238 patients from the present phase III study. As of July 1, 2010, 213 (79.8%) remained in the study and were receiving clobazam. Of these, 189 (89%) had received clobazam for ≥1 year, and 44 of 61 patients from phase II remained in the study approximately 4 years after entry.29 In addition, a retrospective study of 50 treatment responders (patients with intractable epilepsy who experienced ≥75% decreases in seizure frequency after the addition of clobazam to their current AED regimens) found that 43 (86%) remained on clobazam therapy after 1 year, and 39 (78%) remained on clobazam therapy after 5 years.30 This retention of patients on clobazam therapy indicates that patients may continue to have a favorable benefit/risk profile with long-term treatment.

The effect of clobazam on nondrop seizures was not significant as assessed in the prespecified analysis. This study was not designed nor powered to evaluate the effect of clobazam on nondrop seizures. Although most patients had a history of nondrop seizures, patients were not required to have had a minimum number of nondrop seizures during the baseline period to be randomized. As a result, the sample size for nondrop seizure analysis was smaller than for drop seizure analysis.

Several confounding elements make interpretation of these results difficult. Nondrop seizure counts were highly variable by patient and by time point (because of the small sample size) during the course of the study, as evidenced by the finding that patients who received adjunctive placebo (and their stable dosages of AEDs) experienced a substantial worsening (i.e., 76.3% increase) in their nondrop seizure rate. This may be a result of variations in the natural course of LGS.

Clobazam 0.25 mg/kg/day, 0.5 mg/kg/day, and 1.0 mg/kg/day for up to 12 weeks of maintenance therapy was efficacious for patients with LGS aged 2 to 54 years. Its safety profile was similar to what has been observed in clinical studies of clobazam for other epilepsy diseases. Lundbeck Inc. submitted a New Drug Application to the FDA for clobazam in the treatment of LGS in December 2010. With the lack of highly efficacious treatment options for medical management of LGS, clobazam, a 1,5-benzodiazepine, will be clinically helpful as adjunctive therapy for patients with this debilitating disease.

AUTHOR CONTRIBUTIONS

All authors contributed to the conduct of the research, data analysis/interpretation, and development and revision of the manuscript. Drs. Ng and Conry were study investigators and co-chairs of the study’s executive study management committee, which was responsible for providing advice on scientific and medical matters to Lundbeck Inc., as well as the principal investigator, Dr. Drummond, Principal Biostatistician, Lundbeck Inc., managed the biostatistical analyses, which were conducted by biostatisticians at Quintiles Transnational Corp. (Morrisville, NC).

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